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MORPHOLOGY OF TRANSPLANTED LIVER IN RECURRENT PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 2

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Progressive familial intrahepatic cholestasis type 2 (PFIC-2), formerly known as Byler's syndrome, is an autosomal recessive disorder. In infancy or early childhood, this disease leads to end-stage hepatic disease, in which liver transplantation is the only radical treatment. In general, liver transplantation outcomes are good, but in the long term, PFIC-2 may reoccur. We present a case where a girl, aged 28 months, who suffered from cirrhosis resulting from PFIC-2, underwent a related transplantation of the left lateral sector of the liver (her grandmother as the donor). Punch biopsy was performed 8 years after the liver transplant due to graft dysfunction. Histopathology revealed a recurrent PFIC-2. F4. Increased liver failure was the reason for retransplantation of the left lobe of the liver also from a related donor (mother). Pathological pictures in the biopsy specimen and in the liver removed during retransplantation were identical, which once again confirmed PFIC-2 recurrence.

Keywords: recurrent progressive familial intrahepatic cholestasis, PFIC-2, hepatocyte dystrophy, multinucleated cells.

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of diseases with an autosomal recessive inheritance. In PFIC, bile formation is impaired and hepatocellular cholestasis develops. Currently, there are six known types of pyelonephritis [1, 2]. Among them, PFIC type 2 (PFIC-2), formerly known as Byler disease, is characterized by a mutation in the ABCB11 gene, which encodes the BSEP transport protein. Its absence in the canalicular membrane of hepatocytes causes cholestasis and leads to liver fibrosis and end-stage disease in the first decade of life [3].

In PFIC-2, the main clinical symptoms are cholestasis, pruritus, and jaundice. In the blood serum, the activity of gamma-glutamyl transferase is within the normal range [4, 5]. Diagnosis is based on clinical manifestations, liver ultrasound, cholangiography, and liver histology [5]. An analysis of the results of palliative operations in children showed a decrease in pruritus and cholestasis [6–8]. However, liver transplantation remains the uncontested radical treatment method.

In general, the outcomes of liver transplantation in patients that have had PFIC-2 are good [9]. However, more recently, there have been reports that PFIC-2 patients after liver transplantation develop recurrent cholestasis along with clinical and histological signs of primary disease. Recurrence of the disease is associated with the emergence of autoantibodies against the BSEP protein, which inhibits the transport activity of the bile salt pump and causes severe cholestasis [3, 10–13].

This study reports on one of the cases where histological signs of recurrent PFIC-2 were found while examining transplanted liver biopsy specimens.

OWN OBSERVATION

On November 26, 2009, a 28-month-old girl with PFIC-2 cirrhosis underwent a related orthotopic left lateral liver transplantation from her grandmother. The removed native liver weighed 630 g, measured 19 × 15 × 11 × 6 cm, and had a brown-green surface, slightly granular. In the cut, the liver was greenish-brown, the bile ducts, mainly in the area of the gate, were dilated, filled with thick bile and sand.

Histological examination. *The hepatic beam and lobular structure is disturbed. Hepatocytes were 2–3 times enlarged compared to the norm, in a state of marked protein degeneration, necrosis of individual cells (Fig. 1). There was a large number of multinucleated giant cells. Intracellular cholestasis. There was stagnation of bile in the dilated bile capillaries. Foci of accumulation of polynuclear leukocytes and their debris in sinusoids. In the sclerosed portal tracts, the bile ducts were preserved, vascular congestion (Fig. 2). Porto-portal and porto-central septa with insignificant infiltration of lymphoid cells, with an admixture of polynuclear leukocytes and moderately pronounced ductuloneogenesis.* ***Histological diagnosis:*** *liver cirrhosis resulting from PFIC-2.*

The early postoperative period was uneventful. The patient was discharged in a satisfactory condition under outpatient supervision. Graft function remained satis-

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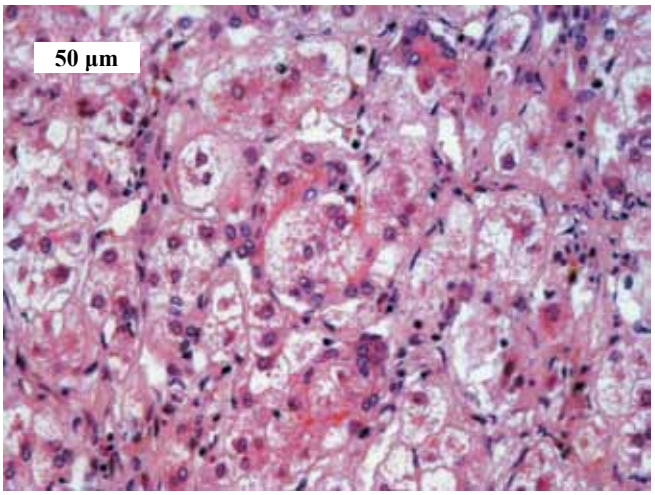

Fig. 1. The girl is 28 months old. Native liver. Giant hepatocyte dystrophy. Visible among them are multinucleated cells. H&E stain. 400× magnification

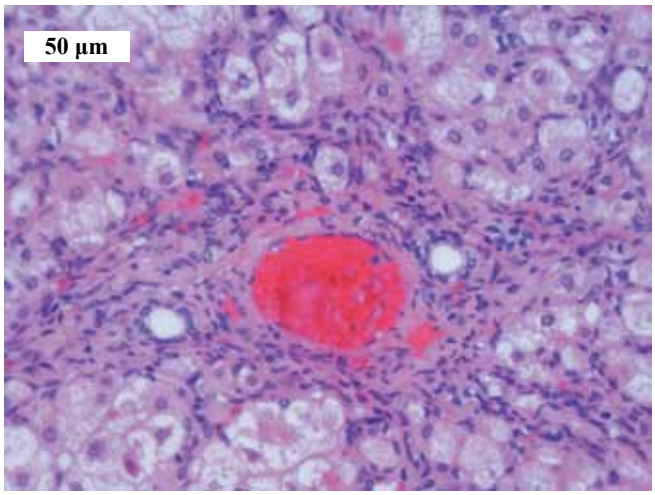

Fig. 2. The girl is 28 months old. Native liver. Red thrombus in the vein of the sclerosed portal tract. Lymphocytic infiltration of the portal tract and septa. F4 (by METAVIR). H&E stain. 400× magnification

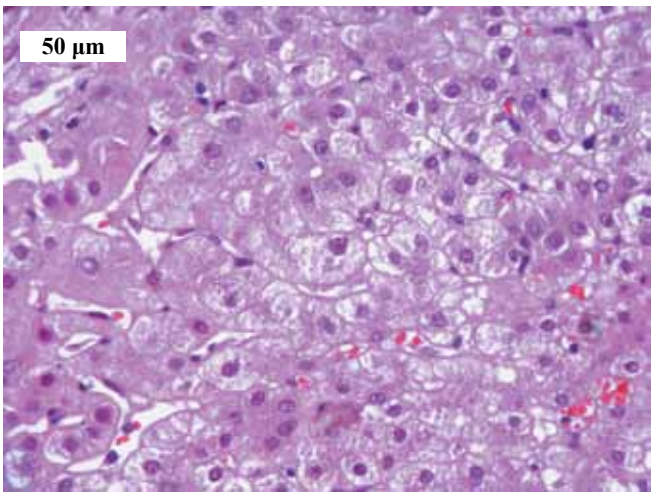

Fig. 3. At 2 years and 8 months after liver transplant. Needle biopsy of the transplanted liver. Giant hepatocyte dystrophy. H&E stain. 400× magnification

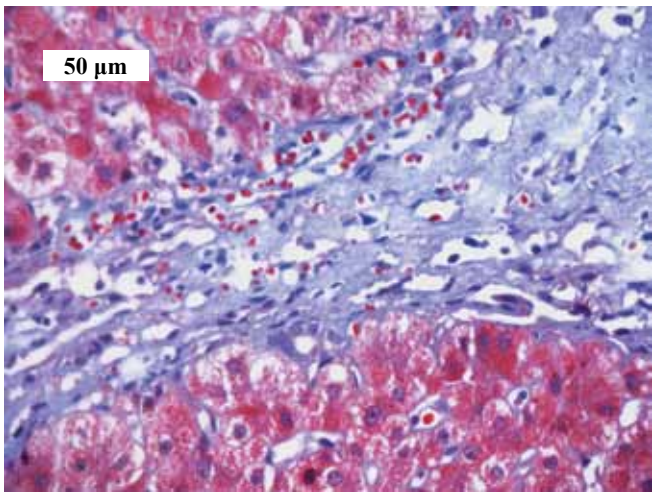

Fig. 4. At 2 years and 8 months after liver transplant. Needle biopsy of the transplanted liver. Sclerosis of the portal tract and septal sclerosis. F2 (by METAVIR). H&E stain. 400× magnification

factory. There were episodes of intercurrent infectious diseases (acute respiratory and intestinal). Routine therapy was administered.

The patient's condition was satisfactory until August 2012. Her immunosuppressive therapy included prograf 1.5 mg per day, methylprednisolone 6 mg per day, and CellCept 500 mg per day. Plasma creatinine level was 19.6 mmol/L, blood plasma urea 2.57 mmol/L, bilirubin 150 mmol/L, AST 67.8, and ALT 59.6. The patient's body weight was 21 kg. The blood level of prograf was 8.8 mg/mL.

Transcutaneous needle biopsy of the transplanted liver was performed on August 2, 2012 due to signs of dysfunction of the transplanted liver. The biopsy specimen showed abnormal lobular and beam structure of the liver, pronounced diffuse protein dystrophy and micro-focal necrosis of hepatocytes (Fig. 3). Porto-portal and porto-central septa with hemorrhages, moderate inflammatory infiltration, mild proliferation of the bile ducts (Fig. 4). Severe perivenular fibrosis of the central vein wall. Focal small-droplet fatty degeneration of hepatocytes.

The patient developed itchy skin from October 2018, with increasing severity. The itching was ruled out to have allergic, mechanical, or infectious origin. By February 13, 2019, clinical-laboratory and imaging signs of liver graft dysfunction were identified. Cytolysis level 1044/1444, total bilirubin level 84, direct bilirubin 44, albumin 28 g/L. Immunosuppression: tacrolimus 2 × 2 times a day. The patient's body weight was 33 kg.

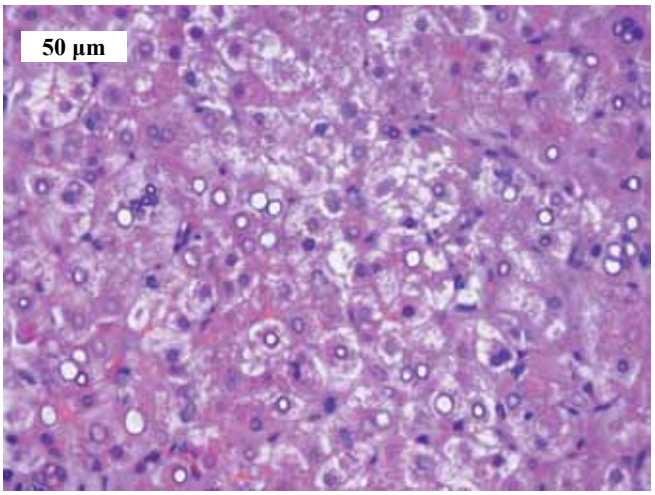

Fig. 5. Material from a needle biopsy of the transplanted liver 8 years and 11 months after surgery. Dystrophic changes not only in the cytoplasm of giant hepatocytes, but also in the nuclei, which look like an "hourglass". H&E stain. 400× magnification

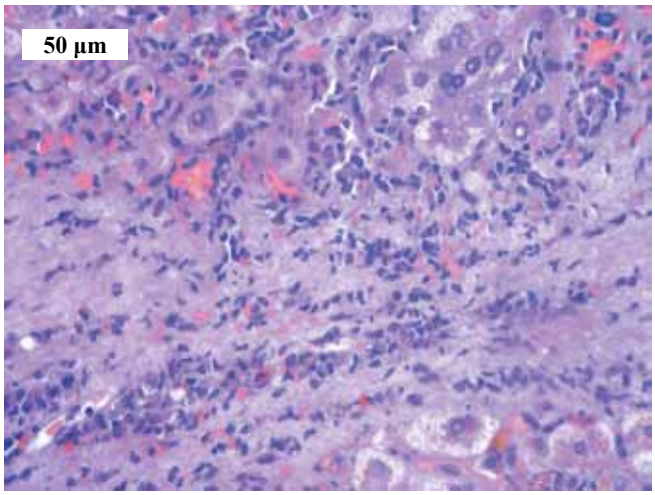

Fig. 6. Material of percutaneous needle biopsy of the transplanted liver at 8 years and 11 months after surgery. Lymphocytic infiltration of the portal tract and septa. F4 (by METAVIR). On the periphery of the septum are giant and multinucleated hepatocytes. H&E stain. 400× magnification

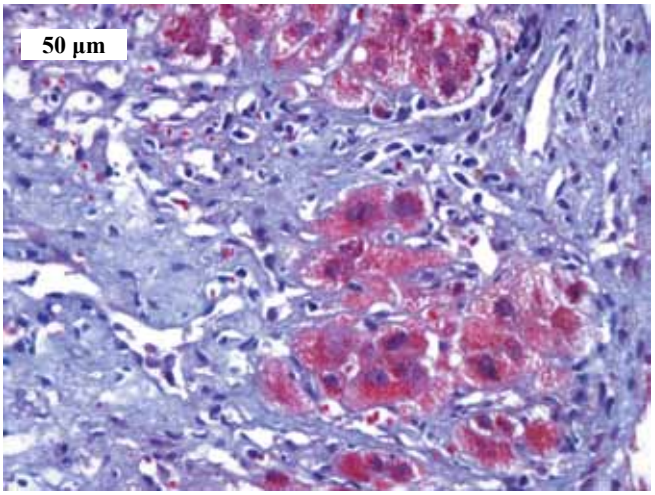

Fig. 7. Material from percutaneous needle biopsy of the transplanted liver at eight years and 11 months after surgery. Dystrophic changes in giant hepatocytes in the false lobules. F4 (by METAVIR). H&E stain. 400× magnification

A second biopsy of the transplanted liver was performed on February 14, 2019. Histological examination found that the changes in the graft were similar to those described in the material of the previous biopsy. The beam and lobular structure of the liver was abnormal. There were severe granular and focal ballooning degeneration of hepatocytes, multinucleated hepatocytes. Unlike the previous biopsy, there was a large number of cells with "sandy" nuclei (Fig. 5). Severe portal tract fibrosis, formation of varying width of porto-portal septa. Portal triads were infiltrated by mononuclear cells, with single newly formed bile ducts; bile duct epithelium was preserved (Fig. 6, 7). There was intracellular accumulation of bile pigment granules, mainly in hepatocytes located periportally, bile stagnation in single small bile ducts. Immunofluorescence revealed small granular deposits of the C4d complement fragment in the portal tracts and in single sinusoids.

Based on the clinical picture and results of needle biopsies of the transplanted liver, a histological diagnosis was made: recurrent PFIC-2. F4.

Thus, the study results showed that 8 years after the liver transplant, the graft developed changes similar to the pathology of its own liver. In this regard, as well as in connection with the increase in liver failure, the girl underwent retransplantation of the left lobe of the liver, also from a related donor (mother) on June 19, 2019. The pathological picture in the biopsy specimen and in the liver removed during retransplantation was identical, which once again confirmed recurrent PFIC-2.

DISCUSSION

Recurrent PFIC-2 is a rare post-liver transplant complication. Only one relatively old publication [14] reported on 6 patients with PFIC-2 who developed a recurrence of the disease. The rest of the publications on this topic are devoted to single cases [3, 10–13].

In our case, it is not possible to determine the timing of the onset of recurrent PFIC-2, since the first clinical signs of transplanted liver failure appeared 2 years and 8 months after the operation. At the same time, the first percutaneous needle biopsy of the graft was performed. Histological examination of a biopsy specimen of the transplanted liver revealed a several-fold increase in the size of hepatocytes due to edema, which was associated with the absence of the BSEP protein, which ensures transport of bile salts from hepatocytes [3, 10–13]. There were also multinucleated hepatocytes, which, according

to literature [13], are a distinctive histological feature of PFIC-2. Intracellular accumulation of bile acids led to development of portal tract sclerosis and appearance of septa (F2). The peculiarity of our case is that the end stage of liver failure developed six and a half years after the appearance of its first signs, when the second biopsy revealed cirrhosis of the graft. Interestingly, hepatocyte pathology in the second biopsy was similar to hepatocyte changes in the much earlier, first biopsy. A distinctive feature was the appearance of a large number of hepatocytes with "sandy nuclei", which, in our opinion, indicates a more severe degeneration.

MAIN PROVISIONS BASED ON THE ABOVE CASE

- Typical histological changes in the transplanted liver upon return of PFIC-2: severe hepatocyte degeneration, a several-fold increase in hepatocyte size, multinucleated hepatocytes.
- Upon return of PFIC-2, the first clinical signs of transplanted liver failure appear according to the histological changes in hepatocytes and the presence of liver fibrosis of at least F2 (according to METAVIR).
- Upon return of PFIC-2, the end-stage of the transplanted liver failure corresponds to the histological picture of liver cirrhosis.

The authors declare no conflict of interest.

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